(FILE 'HOME' ENTERED AT 07:27:40 ON 16 DEC 2004)

FILE 'BIOSIS, MEDLINE, EMBASE, SCISEARCH' ENTERED AT 07:36:03 ON 16 DEC 2004

L1 31527 S INTERLEUKIN-5 OR IL5 OR IL-5 OR (EOSINOPHIL DIFFERENTIATION F
L2 86396 S ANTISENSE
L3 25093 S RNAI OR SIRNA OR RIBOZYME
L4 294757 S ASTHMA OR (AIRWAY HYPERRESPONSIVENESS) OR (PULMONARY INFLAMMA
L5 72 S L1 AND L2 AND L4
L6 3 S L1 AND L2 AND L3 AND L4
L7 46 DUP REM L5 (26 DUPLICATES REMOVED)

=> D L7 IBIB ABS 1-46

L7 ANSWER 1 OF 46 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2004558965 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 15531297
TITLE: Administration of **antisense** phosphorothioate oligonucleotide to the p65 subunit of NF-kappaB inhibits established asthmatic reaction in mice.
AUTHOR: Choi Il-Whan; Kim Dae-Ki; Ko Hyun-Mi; Lee Hern-Ku
CORPORATE SOURCE: Department of Immunology and Medical Research Center for Allergic Immune Diseases, Chonbuk National University Medical School, San 2-20, Chonju, Chonbuk 561-180, Republic of Korea.
SOURCE: International immunopharmacology, (2004 Dec 20) 4 (14) 1817-28.
Journal code: 100965259. ISSN: 1567-5769.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20041109
Last Updated on STN: 20041208

AB The transcription factor, nuclear factor (NF)-kappaB, which transactivates various genes for proinflammatory cytokines and many other immunoregulatory genes, plays an important role in the regulation of various inflammatory diseases including **asthma**. Its increased activation has been demonstrated in the lungs after allergen challenge and in airway epithelial cells and macrophages of asthmatic patients. In the present study, we investigated whether the pretreatment with p65 **antisense** results in a significant inhibition of asthmatic reactions in a mouse model. Mice sensitized and challenged with ovalbumin (OVA) showed typical asthmatic reactions as follows: (1) an increase in the number of eosinophil in bronchoalveolar lavage fluid; (2) a marked influx of inflammatory cells into the lung around blood vessels and airways, and airway luminal narrowing; (3) the development of **airway hyperresponsiveness**; (4) the detection of TNF-alpha and Th2 cytokines, such as IL-4 and **IL-5** in the bronchoalveolar lavage (BAL) fluid; and (5) detection of allergen-specific IgE and IgG in the serum. Two successive intravenous administration of p65 **antisense** before the last airway OVA challenge resulted in a significant inhibition of all asthmatic reactions, whereas the p65 nonsense did not produce such effects. In addition, the p65 **antisense** inhibition of asthmatic reaction appears to be due to the initial suppression of an allergen-specific IgE response, inducing degranulation of mast cells through the cross-linking of allergen-specific IgE. This study may provide evidence that NF-kappaB plays a critical role in the pathogenesis of **asthma** in mice.

L7 ANSWER 2 OF 46 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004393986 EMBASE
TITLE: Newer drugs for **asthma**.
AUTHOR: Singh M.
CORPORATE SOURCE: Dr. M. Singh, Department of Pediatrics, Advanced Pediatrics Centre, Post Grad. Inst. of Med. Educ./Res., Chandigarh, India. meenusingh4@rediffmail.com
SOURCE: Indian Journal of Pediatrics, (2004) 71/8 (721-727).
Refs: 25
ISSN: 0019-5456 CODEN: IJPEA2
COUNTRY: India
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Several new drugs have resulted from innovative pharmacological and immunomodulatory approaches towards treatment of **asthma**. Diverse therapeutic targets have provided new agents. The new classes of drugs available are newer "on site activated inhaled corticisteroids" and soft steroids, anti IgE compounds, leukotriene inhibitors and single isomer agents which are available for clinical use. Anti interleukin agents and phosphodiesterase inhibitors are in the stage of clinical trials. **Antisense** therapy and pharmacogenetics are the on horizon for treatment of **asthma**.

L7 ANSWER 3 OF 46 MEDLINE on STN
ACCESSION NUMBER: 2004411461 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15316505
TITLE: Inhibition of signal transducer and activator of transcription 1 attenuates allergen-induced airway inflammation and hyperreactivity.
AUTHOR: Quarcoo David; Weixler Silke; Groneberg David; Joachim Ricarda; Ahrens Birgit; Wagner Andreas H; Hecker Markus; Hamelmann Eckard
CORPORATE SOURCE: Department of Pediatric Pneumology and Immunology, Charite-Humboldt University, Berlin, Germany.
SOURCE: Journal of allergy and clinical immunology, (2004 Aug) 114 (2) 288-95.
Journal code: 1275002. ISSN: 0091-6749.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200409
ENTRY DATE: Entered STN: 20040819
Last Updated on STN: 20040917
Entered Medline: 20040916
AB BACKGROUND: Transcriptional factors of the signal transducer and activator of transcription (STAT) family play an important role in orchestrating immune reactions. OBJECTIVE: The aim of the current study was to investigate the role of STAT-1 in murine allergen-induced sensitization and development of airway inflammation (AI) and airway hyperreactivity (AHR), cardinal features of bronchial **asthma**. METHODS: BALB/c mice were systemically sensitized to ovalbumin and challenged with ovalbumin through the airways. Decoy oligonucleotide (ODN) specific for STAT-1 was applied once locally to the airways of sensitized animals before allergen airway challenges. RESULTS: Single application of decoy ODN markedly and significantly reduced numbers of eosinophils and

lymphocytes in bronchoalveolar lavage fluids compared with those seen in sensitized and challenged animals receiving mutant control ODN. Associated with this decrease in eosinophilic AI were significantly reduced levels of **IL-5** in BAL fluid, of CD40 expression in peribronchial infiltrates, and of vascular cell adhesion molecule 1 expression in vascular endothelial cells, respectively. In addition, development of AHR after allergen sensitization and airway challenges was effectively abolished after local STAT-1 decoy ODN treatment. CONCLUSION: The data indicate that a decoy ODN neutralizing STAT-1 effectively inhibits allergen-induced AI and AHR, probably by attenuating upregulation of costimulatory and adhesion molecules, and suggest a significant role of STAT-1 in **asthma** pathology.

L7 ANSWER 4 OF 46 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004112113 EMBASE
TITLE: Biochemical Assessment of Intracellular Signal Transduction Pathways in Eosinophils: Implications for Pharmacotherapy.
AUTHOR: Wong C.K.; Ip W.K.; Lam C.W.K.
CORPORATE SOURCE: Prof. C.W.K. Lam, Department of Chemical Pathology, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, NT, Hong Kong. waikeilam@cuhk.edu.hk
SOURCE: Critical Reviews in Clinical Laboratory Sciences, (2004) 41/1 (79-113).
Refs: 192
ISSN: 1040-8363 CODEN: CRCLBH
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Allergic **asthma** and allergic rhinitis are inflammatory diseases of the airway. Cytokines and chemokines produced by T helper (Th) type 2 cells (GM-CSF, IL-4, **IL-5**, IL-6, IL-9, IL-10 and IL-13), eotaxin, transforming growth factor-β, and IL-11 orchestrate most pathophysiological processes of the late-phase allergic reaction, including the recruitment, activation, and delayed apoptosis of eosinophils, as well as eosinophilic degranulation to release eosinophilic cationic protein, major basic protein, and eosinophil-derived neurotoxin. These processes are regulated through an extensive network of interactive intracellular signal transduction pathways that have been intensively investigated recently. Our present review updates the cytokine and chemokine-mediated signal transduction mechanisms including the RAS-RAF-mitogen-activated protein kinases, Janus kinases (signal transducers and activators of transcription), phosphatidylinositol 3-kinase, nuclear factor-kappa B, activator protein-1, GATA, and cyclic AMP-dependent pathways, and describes the roles of different signaling pathways in the regulation of eosinophil differentiation, recruitment, degranulation, and expression of adhesion molecules. We shall also discuss different biochemical methods for the assessment of various intracellular signal transduction molecules, and various antagonists of receptors, modulators, and inhibitors of intracellular signaling molecules, many of which are potential therapeutic agents for treating allergic diseases.

L7 ANSWER 5 OF 46 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 2

ACCESSION NUMBER: 2004:94220 BIOSIS
DOCUMENT NUMBER: PREV200400094167
TITLE: Inhibition of **antisense**-endothelin converting enzyme RNA on **interleukin-5** released

from dust mite-challenged peripheral blood mononuclear cells in patients with allergic **asthma**.

AUTHOR(S): Li Li [Reprint Author]; Xu Ju [Reprint Author]; Zhong Nan-shan [Reprint Author]

CORPORATE SOURCE: Institute of Respiratory Diseases, Affiliated First Hospital, Guangzhou Medical College, Guangzhou, 510120, China

SOURCE: Zhonghua Jiehe He Huxi Zazhi, (September 2003) Vol. 26, No. 9, pp. 531-534. print.
ISSN: 1001-0939.

DOCUMENT TYPE: Article

LANGUAGE: Chinese

ENTRY DATE: Entered STN: 11 Feb 2004
Last Updated on STN: 11 Feb 2004

AB Objective: To investigate the effect of **antisense** endothelin converting enzyme (ECE) RNA on levels of cytokines released from CD4+ lymphocytes in patients with allergic diseases responsive to house dust mites. Methods: Peripheral blood mononuclear cells (PBMCs) were separated from 21 patients who were sensitive to dust mites. PBMCs from those patients were divided into two groups. No stimulation group (A group) included A1 group (anti-ECE epithelial cells+PBMCs) and A2 group (control cells+PBMCs). Stimulation group (B group) included B1 group (anti-ECE epithelial cells+PBMCs+dust mites extract) and B2 group (control cells+PBMCs+dust mites extract). House dust mite extract (20 mug/ml) was added to the culture of stimulation group as described above. After 72 hours, supernatants from both groups were collected and the levels of **IL-5** and IFN-gamma released into the supernatants were detected by enzyme-linked immunoabsorbent assay. Results: **IL-5** levels were increased significantly after treatment with dust mite in twelve of 21 cases. No significant differences of **IL-5** were found between the groups of A1((6.0+-1.3)X10-9 g/L) and A2((7.5+-1.1)X10-9 g/L) before house dust mite stimulation in the 12 cases (P>0.05), and no significant differences in IFN-gamma were found between the groups of A1((63+-26)X10-9 g/L) and A2((70+-52)X10-9 g/L) before house dust mite stimulation (P>0.05). **IL-5** level was increased in both groups after stimulation but it was significantly lower in the B1 group ((8.2+-1.6)X10-9 g/L) than that in the B2((12.0+-1.8)X10-9 g/L) (P=0.047). It seemed that increased IFN-gamma level after stimulation was higher in B2((153+-71)X10-9 g/L) than that in the B1 group (100+-41)X10-9 g/L), but there was no statistic significance (P>0.05). In addition, our results also showed that the release of **IL-5** was significantly increased in those cases with **asthma**, or **asthma** plus allergic rhinitis after dust mites stimulation ((44+-15)%) compared with that in those with urticaria ((7+-4)%) (P=0.047). Conclusions: **Antisense**-ECE downregulated the **IL-5** secretion from Th2 lympocytes in patients with allergic **asthma** after being challenged with dust mites. It is indicated that ET-1 is an important cytokine involved with allergic airway inflammation. **Antisense**-ECE RNA management in airways maybe of value in treating allergic **asthma**.

L7 ANSWER 6 OF 46 MEDLINE on STN DUPLICATE 3

ACCESSION NUMBER: 2004053777 MEDLINE

DOCUMENT NUMBER: PubMed ID: 14754517

TITLE: New **asthma** drugs acting on gene expression.

AUTHOR: Popescu F-D

CORPORATE SOURCE: Department of Allergology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania..
florindanpopescu@hotmail.com

SOURCE: Journal of cellular and molecular medicine, (2003 Oct-Dec) 7 (4) 475-86. Ref: 31
Journal code: 101083777. ISSN: 1582-1838.

PUB. COUNTRY: Romania
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200404
ENTRY DATE: Entered STN: 20040203
Last Updated on STN: 20040416
Entered Medline: 20040415

AB New **asthma** drugs acting on transcription are transcription factor agonists (dissociated steroids, peroxisome proliferator-activated receptor gamma agonists), transcription factor inhibitors (NF-kappaB / AP-1 inhibitors, STAT6 inhibitors), inhibitors of protein kinases acting on transcription factors (p38 MAP kinase inhibitors), and chromatin modifying agents. Pharmacological approach of translation in **asthma** includes therapeutic ribozymes and **antisense** oligonucleotides targeting receptors (adenosine A1 receptor, alpha chain of **IL-5** receptor, common beta chain of IL-3/**IL-5**/GM-CSF receptor), cytokines (IL-4, **IL-5**, SCF), signal transduction molecules (Syk, Lyn), transcription factors (STAT-6, GATA-3). Some of these drugs acting on gene expression have the potential to improve therapeutic benefits compared with traditional drugs.

L7 ANSWER 7 OF 46 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003304186 EMBASE
TITLE: T helper type-2 cytokine responses: Potential therapeutic targets.
AUTHOR: Jarnicki A.G.; Fallon P.G.
CORPORATE SOURCE: P.G. Fallon, Department of Biochemistry, Trinity College, Dublin 2, Ireland. pfallon@tcd.ie
SOURCE: Current Opinion in Pharmacology, (2003) 3/4 (449-455).
Refs: 57
ISSN: 1471-4892 CODEN: COPUBK
PUBLISHER IDENT.: S 1471-4892(03)00077-8
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB T helper (Th)2 cell-mediated immune responses are associated with parasitic helminth infections and atopic disorders. The production of interleukin (IL)-4, **IL-5**, IL-9 and/or IL-13 by Th2 cells mediates a range of responses that can be protective or pathogenic. Progress has recently been made in elucidating the mechanism of Th2 immunity, which has therapeutic potential for the treatment of allergic diseases.

L7 ANSWER 8 OF 46 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003114483 EMBASE
TITLE: New and exploratory therapies for **asthma**.
AUTHOR: Boushey H.A.
CORPORATE SOURCE: Dr. H.A. Boushey, Box 0130, 1292-M, Univ. of California San Francisco, 505 Parnassus Ave, San Francisco, CA 94143-0130, United States. hab2@itsa.ucsf.edu
SOURCE: Chest, (1 Mar 2003) 123/3 SUPPL. (439S-445S).

Refs: 55
ISSN: 0012-3692 CODEN: CHETBF
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB **Asthma** treatment is certain to undergo revolutionary changes. It is hazardous to speculate, but it seems possible that we will soon have ways to prevent common allergies through the induction of tolerance by manipulating the type, route, timing, intensity, and conditions of exposure to common sensitizing antigens. It is, however, still unclear whether the induction of allergic mechanisms of response in the airways is sufficient to cause **asthma**. There may be some additional mechanism that would be more effectively targeted by a new therapy, perhaps STAT1 upregulation in epithelium, or bronchial mast cell proliferation. The development of new ways of selectively inhibiting the production of specific mediators, as through delivery of **antisense** DNA, offers new weapons to attack new targets. And it may be that searching for a single target will be fruitless, for the components of the **asthma** phenotype - bronchial hyperreactivity, mucus hypersecretion, eosinophilic inflammation, hyperplasia of structural cells, increase in extracellular matrix, and deposition of collagen - may prove to be independently regulated, especially in patients with established disease. About all that can be said with certainty is that we do not now lack for targets, and more are sure to be suggested by continuing research on the mechanisms of allergic sensitization, on interactions between genotype and the environment, and on the actions of infecting organisms.

L7 ANSWER 9 OF 46 EMBASE
on STN DUPLICATE 4
ACCESSION NUMBER: 2003256919 EMBASE
TITLE: Recent developments in clinical trials for bronchial **asthma**.
AUTHOR: Nakagawa T.
CORPORATE SOURCE: Dr. T. Nakagawa, Department of Internal Medicine, St. Marianna Univ. Toyoko Hospital, 3-435 Kosugi-cho, Nakahara-ku, Kawasaki, 211-0063, Japan. tnakagaw@marianna-u.ac.jp
SOURCE: Methods and Findings in Experimental and Clinical Pharmacology, (2003) 25/4 (311-315).
Refs: 42
ISSN: 0379-0355 CODEN: MFEPDX
COUNTRY: Spain
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Bronchial **asthma** is a chronic inflammatory disorder of the airways. Currently available antiinflammatory treatments, represented by inhaled corticosteroids (ICS), are highly effective in controlling symptoms ill the majority of patients, but their potential side effects have led to the use of adjunctive or alternative therapies and to the development of new therapies. Most of these new agents are aimed at

inhibiting various components of allergic inflammation, with better safety profiles than ICS. They include inhibitors of phosphodiesterase 4, cytokine modulators, chemokine receptor antagonists and **antisense** oligonucleotides. .COPYRGT. 2003 Prous Science. All righls reserved.

L7 ANSWER 10 OF 46 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004328923 EMBASE
TITLE: Significant involvement of CCL2 (MCP-1) in inflammatory disorders of the lung.
AUTHOR: Rose Jr. C.E.; Sung S.-S.J.; Fu S.M.
CORPORATE SOURCE: Dr. C.E. Rose Jr., Univ. of Virginia School of Medicine, Charlottesville, VA 22908, United States. CER@VIRGINIA.EDU
SOURCE: Microcirculation, (2003) 10/3-4 (273-288).
Refs: 97
ISSN: 1073-9688 CODEN: MROCER
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Mounting evidence suggests that CCL2 (MCP-1) and its hematopoietic cell receptor CC chemokine receptor 2 (CCR2) are involved in inflammatory disorders of the lung. In animal models of allergic **asthma**, idiopathic pulmonary fibrosis (IPF), and bronchiolitis obliterans syndrome (BOS), CCL2 expression and protein production are increased and the disease process is attenuated by CCL2 immunoneutralization. Mechanisms by which CCL2 may be acting include recruitment of regulatory and effector leukocytes; stimulation of histamine or leukotriene release from mast cells or basophils; induction of fibroblast production of transforming growth factor-β (TGF-β) and procollagen; and enhancement of Th2 polarization. Recently, polymorphism for CCL2 has been described with increased cytokine-induced release of CCL2 by monocytes and increased risk of allergic **asthma**. These studies identify potentially important roles for CCL2 in these lung inflammatory disorders. While CCL2 inhibition in patients with acute respiratory distress syndrome (ARDS) may be hazardous by interfering with defense against bacteremia, future studies are needed to determine if CCL2/CCR2 antagonism will offer breakthrough therapy for patients with allergic **asthma**, IPF, or BOS, and to confirm the hypothesis that CCL2 polymorphism places patients at greater risk for these disorders. .COPYRGT. 2003 Nature Publishing Group.

L7 ANSWER 11 OF 46 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003142336 EMBASE
TITLE: Gene therapy for **asthma**.
AUTHOR: Factor P.
CORPORATE SOURCE: P. Factor, Sec. of Pulmonary/Critical Care Med., Evanston Northwestern Healthcare, Northwestern Univ. Feinberg Sch. Med, 2650 Ridge Rd., Evanston, IL 60201, United States. pfactor@northwestern.edu
SOURCE: Molecular Therapy, (1 Feb 2003) 7/2 (148-152).
Refs: 35
ISSN: 1525-0016 CODEN: MTOHCK
COUNTRY: United States
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 005 General Pathology and Pathological Anatomy

015 Chest Diseases, Thoracic Surgery and Tuberculosis
022 Human Genetics
026 Immunology, Serology and Transplantation
037 Drug Literature Index
039 Pharmacy

LANGUAGE: English
SUMMARY LANGUAGE: English

AB The accessibility of the airway epithelium and the limitations of current treatments for **asthma** make the disease a logical target for gene therapy. Study of the immunopathology of chronic airway inflammation has recently identified several pathways that lead to the maladaptive, antigen-induced polarization of CD4+ T cells to a type-2 phenotype. This polarization is thought to lead to IgE production and eosinophil recruitment and activation that is associated with epithelial cell injury and airway hyper-reactivity. Gene transfer to the bronchial epithelium has been used in experimental models to redirect these pathways toward a less injurious, type-1 phenotype. This mini-review highlights recent mechanism-based immunomodulatory and supportive gene transfer approaches to treat animal models of **asthma**. Although substantial hurdles to airway gene transfer remain, gene transfer offers the possibility of interrupting the patho-physiology of airway inflammation. Doing so can be expected to yield long-lasting protection from bronchospastic challenge and reduced dependence on inhaled and oral medications.

L7 ANSWER 12 OF 46 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2003:566820 BIOSIS
DOCUMENT NUMBER: PREV200300563849
TITLE: Local delivery of a B7.2-specific **antisense** oligonucleotide inhibits airway inflammation and hyperresponsiveness in mice.
AUTHOR(S): Crosby, J. R. [Reprint Author]; Witchell, D. W. [Reprint Author]; Arberg, C. C. [Reprint Author]; Shen, L. [Reprint Author]; McKay, K. [Reprint Author]; Monia, B. P. [Reprint Author]; Karras, J. G. [Reprint Author]; Gregory, S. A. [Reprint Author]; Tung, D. [Reprint Author]
CORPORATE SOURCE: 2292 Faraday Avenue, Carlsbad, CA, 92008, USA
SOURCE: Inflammation Research, (July 2003) Vol. 52, No. Supplement 2, pp. S 85. print.
Meeting Info.: 6th World Congress on Inflammation. Vancouver, British Columbia, Canada. August 02-06, 2003. International Association of Inflammation Societies.
ISSN: 1023-3830.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Dec 2003
Last Updated on STN: 3 Dec 2003

L7 ANSWER 13 OF 46 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 5

ACCESSION NUMBER: 2002:269657 BIOSIS
DOCUMENT NUMBER: PREV200200269657
TITLE: Inhibition of antigen-induced eosinophilia and **airway hyperresponsiveness** by **antisense** oligonucleotides directed against the common beta chain of IL-3, **IL-5**, GM-CSF receptors in a rat model of allergic **asthma**.
AUTHOR(S): Allakhverdi, Zoulfia; Allam, Mustapha; Renzi, Paolo M. [Reprint author]
CORPORATE SOURCE: CHUM Research Center, 2065 Alexandre de Seve, 8th floor, Montreal, Quebec, H2L 2W5, Canada

renzip@earthlink.net
SOURCE: American Journal of Respiratory and Critical Care Medicine, (April 1, 2002) Vol. 165, No. 7, pp. 1015-1021. print. ISSN: 1073-449X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 1 May 2002
Last Updated on STN: 1 May 2002

AB Airway obstruction, hyperresponsiveness, and the accumulation and persistence within the airways of inflammatory cells characterize **asthma**. Interleukin (IL)-3, granulocyte macrophage colony-stimulating factor (GM-CSF), and **IL-5** are among several cytokines that have been shown to be increased in **asthma** and to contribute to atopic inflammation. They mediate their effect via receptors that have a common beta subunit (betac). We hypothesized that blocking of this common betac would impair the airway response to antigen. We report that an **antisense** (AS) phosphorothioate oligodeoxynucleotide (ODN) found to specifically inhibit transcription of the betac in rat bone marrow cells also caused inhibition of betac mRNA expression and of immunoreactive cells within the lungs of Brown Norway (BN) rats when injected intratracheally ($p < 0.01$). Inhibition of betac significantly reduced ($p < 0.01$) experimentally induced eosinophilia in vivo in ovalbumin (OVA)-sensitized BN rats after antigen challenge. Furthermore, when compared with mismatch-treated rats, betac AS-ODN caused inhibition of antigen-induced **airway hyperresponsiveness** to leukotrine D4. Taken together, our findings demonstrate that the common betac of IL-3, **IL-5**, and GM-CSF receptors is involved in the eosinophil influx and **airway hyperresponsiveness** that follow OVA challenge and underscore the potential utility of a topical **antisense** approach targeting betac for the treatment of **asthma**.

L7 ANSWER 14 OF 46 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004048426 EMBASE
TITLE: Mucosal Immunology - 11th International Congress: 16-20 June 2002, Orlando, FL, USA.
AUTHOR: Cyr S.
CORPORATE SOURCE: S. Cyr, ID Biomedical Quebec, 7150 Frederick Banting, Suite 200, Ville St-Laurent, Que. H4S 2A1, Canada. csonya@intellivax.com
SOURCE: IDrugs, (2002) 5/8 (753-756). ISSN: 1369-7056 CODEN: IDRUFN
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 037 Drug Literature Index
017 Public Health, Social Medicine and Epidemiology
026 Immunology, Serology and Transplantation
004 Microbiology
030 Pharmacology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The 11th International Congress of Mucosal Immunology was held at the Wyndham Palace Resort and Spa in Orlando, from the 16th to 20th June 2002. The meeting attracted scientists and clinicians interested in the many areas relevant to mucosal immunology. Researchers presented fundamental developments as well as research relating to potential vaccine or drug candidates. There were a number of prominent presentations related to prophylaxis and therapy, including: (i) 'Adjuvantation of mucosal vaccines against model antigens, HIV, respiratory syncytial virus (RSV) and influenza'; (ii) 'Adjuvant mechanisms'; (iii) 'Mechanisms and therapy'; (iv) 'Allergy prophylaxis and treatment'; (v) 'Maintenance of mucosal

immunity and aging'; and (vi) 'Routes of delivery'. Recent advances in mucosal vaccines and treatment combined with promising research on immune mechanisms contribute to positioning mucosal immunology at the forefront of the pharmaceutical industry's agenda. The pharmaceutical industry was well represented at the meeting with several large companies (eg, Wyeth, Chiron Corp, AstraZeneca plc, Aventis SA and Johnson & Johnson) presenting abstracts or participating in research collaboration. .COPYRGT. PharmaPress Ltd.

L7 ANSWER 15 OF 46 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2002:737359 SCISEARCH
THE GENUINE ARTICLE: 588ZZ
TITLE: Gene therapy with galectin-3 inhibits bronchial obstruction and inflammation in antigen-challenged rats through **interleukin-5** gene downregulation
AUTHOR: del Pozo V; Rojo M; Rubio M L; Cortegano I; Cardaba B; Gallardo S; Ortega M; Civantos E; Lopez E; Martin-Mosquero C; Peces-Barba G; Palomino P; Gonzaez-Mangado N; Lahoz C (Reprint)
CORPORATE SOURCE: Fdn Jimenez Diaz, Dept Immunol, Ave Reyes Catolicos 2, E-28040 Madrid, Spain (Reprint); Fdn Jimenez Diaz, Dept Immunol, E-28040 Madrid, Spain; Fdn Jimenez Diaz, Dept Pulmonol, E-28040 Madrid, Spain
COUNTRY OF AUTHOR: Spain
SOURCE: AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE (1 SEP 2002) Vol. 166, No. 5, pp. 732-737.
Publisher: AMER THORACIC SOC, 1740 BROADWAY, NEW YORK, NY 10019-4374 USA.
ISSN: 1073-449X.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 48

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The pathophysiology of **asthma** involves an intricate network of molecular and cellular interactions. Elevated Th2 cytokines (interleukin [**IL**]-**5** and IL-4) associated with eosinophilic inflammation characterize allergic diseases and provide potential targets for immunomodulation. Recent evidence has demonstrated that galectin-3 induces selective downregulation of **IL-5** gene expression in several cell types (eosinophils, T cell lines, and antigen specific T cells). Accordingly, we sought to elucidate whether in vivo intratracheal instillation of plasmid DNA encoding galectin-3 would inhibit an experimental asthmatic reaction in a rat model with increased eosinophils and T cells in bronchoalveolar fluid and impaired pulmonaryfunction. We found that instillation of galectin-3 gene in these rats led to normalization of the eosinophil and T cell count in bronchoalveolar lavage fluid and that there was a strong concomitant inhibition of **IL-5** mRNA in the lungs. As a consequence, galectin-3-treated rats showed recovery of pulmonary functional parameters, such as pulmonary pressure and expiratory flows. These data emphasize the potential utility of galectin-3 as a novel therapeutic approach for treatment of allergic **asthma**.

L7 ANSWER 16 OF 46 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003037963 EMBASE
TITLE: Respirable **antisense** oligonucleotides: A new, third drug class targeting respiratory disease.
AUTHOR: Nyce J.
CORPORATE SOURCE: Dr. J. Nyce, EpiGenesis Pharmaceuticals, Inc., 7 Clarke

Drive, Cranbury, NJ 08512, United States. JNyce@epigene.com
SOURCE: Current Opinion in Allergy and Clinical Immunology, (1 Dec 2002) 2/6 (533-536).
Refs: 23
ISSN: 1528-4050 CODEN: COACCS
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
026 Immunology, Serology and Transplantation
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Purpose of review: To describe the potential of a new class of respiratory drugs, respirable **antisense** oligonucleotides. Recent findings: The first respirable **antisense** oligonucleotide, EPI-2010, has now reached clinical trials. It has shown intriguing initial indications of efficacy and the potential to be the first once-per-week **asthma** preventative. Respirable **antisense** oligonucleotides are capable of addressing targets that have proven to be intractable to traditional 'small molecule' approaches, and against which newer monoclonal antibody strategies may also not be optimal. Respirable **antisense** oligonucleotides functionally, but not genetically, ablate gene expression by blocking the template function of target respiratory messenger RNAs by as yet incompletely defined mechanisms. They do so with an avidity and specificity which can be several orders of magnitude greater than those shown by small molecule antagonists for their protein targets. The target properties of respiratory messenger RNAs are strikingly different from those of respiratory proteins, enabling respirable **antisense** oligonucleotides to offer the potential of longer duration of effect, increased specificity of effect, and lack of systemic side effects compared with either traditional small molecule protein antagonists or monoclonal antibodies. Summary: Respirable **antisense** oligonucleotides represent a new, third class of respiratory drugs with the potential to extend the range of therapeutic responses to otherwise intractable respiratory targets, and to address precedented targets with the possibility of improving on such features as safety and durability of response. .COPYRGT. 2002 Lippincott Williams & Wilkins.

ACCESSION NUMBER: 2004048445 EMBASE
TITLE: American Academy of Allergy, **Asthma** and Immunology: Gene transfer and transcription factors: 1-6 March, 2002, New York City, NY, USA.
AUTHOR: Mohapatra S.S.
CORPORATE SOURCE: S.S. Mohapatra, Div. of Allergy and Immunology, Dept. of Med. Microbiology/Immunol., University of South Florida, 12901 Bruce B Downs Boulevard, Tampa, FL 33612-4799, United States. smohapat@hsc.usf.edu
SOURCE: IDrugs, (2002) 5/4 (312-315).
ISSN: 1369-7056 CODEN: IDRUFN
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 022 Human Genetics
015 Chest Diseases, Thoracic Surgery and Tuberculosis
037 Drug Literature Index
029 Clinical Biochemistry
026 Immunology, Serology and Transplantation
030 Pharmacology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Overall, these symposia focused on two timely themes: one on evaluation of the potential of gene therapy approaches for **asthma**, and the other on the potential of inhibitors of transcription factors and kinases for **asthma** treatment on the basis of the mechanistic understanding of the roles of various pathways involved in pathogenesis and protection. Clearly there appears to be a lot of potential, but we are only beginning to understand these mechanisms and whether or not targeting some of these molecules and pathways for novel **asthma** treatments is useful, only time will tell.

L7 ANSWER 18 OF 46 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 6

ACCESSION NUMBER: 2002:406489 BIOSIS
DOCUMENT NUMBER: PREV200200406489
TITLE: **Asthma** therapy in the new millennium.
AUTHOR(S): Pahl, A. [Reprint author]; Szelenyi, I.
CORPORATE SOURCE: Department of Experimental and Clinical Pharmacology and Toxicology, Friedrich-Alexander-University of Erlangen, Fahrstr. 17, DE-91054, Erlangen, Germany
pahl@pharmakologie.uni-erlangen.de
SOURCE: Inflammation Research, (June, 2002) Vol. 51, No. 6, pp. 273-282. print.
ISSN: 1023-3830.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Jul 2002
Last Updated on STN: 24 Jul 2002

AB Bronchial **asthma** is one of the most common chronic diseases in modern society and yet, despite the availability of highly effective drugs, there is increasing evidence to suggest that its incidence is increasing. It is a general health problem in several industrialised countries and will remain one for the next decades. With regard to **asthma** pathogenesis, our understanding has increased tremendously over the last two decades. Therefore, the potential for specific targeted and constructed therapies has become evident. Monoclonal antibodies to IgE, soluble receptors or antibodies to certain cytokines such as IL-4 and **IL-5** are being investigated as possible treatments for **asthma**. Besides the already known receptor antagonists, new compounds directed to novel receptor types (e.g. cytokine, adenosine, adhesion molecules, etc.) are now under development. New targets in the cytosol will come into focus. Preliminary studies of selective phosphodiesterase (PDE) inhibitors in asthmatic patients have been encouraging. It is also very likely that the use of glucocorticoids cannot be excluded from therapy. However, we should generate new glucocorticoids with less side-effects, probably by using the so-called retrometabolic drug design. The first representative of this new steroid class, loteprednol is already approved for the therapy of certain allergic disorders. Because **asthma** is a disease of many different gene polymorphisms, gene therapy seems to be of low success at present. Alternatively, **antisense** oligonucleotides could be used. Future developments may also include strategies targeting the remodeling of structural elements of the airways. Today's intensive search for new treatments should ensure a greater diversity of therapeutic possibilities for the management of **asthma** in the next millennium.

L7 ANSWER 19 OF 46 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003036568 EMBASE
TITLE: Therapeutic prospects for early **asthma**.
AUTHOR: Anderson G.P.
CORPORATE SOURCE: Prof. Dr. G.P. Anderson, Department of Medicine, University

of Melbourne, Lung Disease Research Group, Parkville, Vic. 3010, Australia. gpa@unimelb.edu.au

SOURCE: Medical Journal of Australia, (16 Sep 2002) 177/6 SUPPL. (S66-S69).
Refs: 11
ISSN: 0025-729X CODEN: MJAUAJ

COUNTRY: Australia
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
038 Adverse Reactions Titles
030 Pharmacology
037 Drug Literature Index
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
005 General Pathology and Pathological Anatomy
LANGUAGE: English

L7 ANSWER 20 OF 46 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2002002602 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11753121
TITLE: Eosinophils, eosinophilic cytokines (**interleukin-5**), and antieosinophilic therapy in **asthma**
.
AUTHOR: Menzies-Gow Andrew; Robinson Douglas S
CORPORATE SOURCE: Department of Allergy and Clinical Immunology, Imperial College School of Medicine at the National Heart and Lung Institute, London, United Kingdom.
SOURCE: Current opinion in pulmonary medicine, (2002 Jan) 8 (1) 33-8. Ref: 31
Journal code: 9503765. ISSN: 1070-5287.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20020102
Last Updated on STN: 20020207
Entered Medline: 20020206

AB Eosinophils are believed to be key effector cells in producing the bronchial mucosal inflammation characteristic of allergic **asthma**
. Given the perceived importance of eosinophils in allergic inflammation, they have been logical therapeutic targets. As knowledge of eosinophil biology increases, eosinophils are targeted with specific therapies blocking their maturation, activation, and chemotaxis. Therapeutic targets include eosinophil-specific cytokines, primarily **interleukin-5**, and chemokines, eg, eotaxin.Several studies over the last year have reported on therapies effective at reducing eosinophil numbers in asthmatics, including two humanized monoclonal antibodies against **interleukin-5** and recombinant human interleukin-12. Surprisingly, despite their effectiveness at depleting eosinophils, there was no evidence of clinical improvement in any of the parameters studied. These and all other relevant studies published within the last year are reviewed by this article. After publication of these studies, some commentators questioned the role of eosinophils in allergic inflammation. Current evidence for and against eosinophils as effector cells in **asthma** is reviewed.

L7 ANSWER 21 OF 46 EMBASE on STN
ACCESSION NUMBER: 2002016223 EMBASE

TITLE: [Coming on immunumodulation and gene therapy. New treatments for **asthma**].
IMMUUNMODULATIE EN GENTHERAPIE IN OPMARS.
AUTHOR: Jonkers R.E.
CORPORATE SOURCE: Dr. R.E. Jonkers, Afdeling Longziekten, Academisch Medisch Centrum, F5-161, Postbus 22.660, 1100 DD Amsterdam, Netherlands. E.jonkers@amc.uva.nl
SOURCE: Pharmaceutisch Weekblad, (4 Jan 2002) 137/1 (27-31).
Refs: 20
ISSN: 0031-6911 CODEN: PHWEAW
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
022 Human Genetics
026 Immunology, Serology and Transplantation
027 Biophysics, Bioengineering and Medical Instrumentation
037 Drug Literature Index
LANGUAGE: Dutch
SUMMARY LANGUAGE: English; Dutch

AB New treatments modalities have been developed on the basis of better understanding of the pathogenesis of **asthma**. These include synthetic proteins based on recombinant DNA, monoclonal antibodies directed against specific elements in the inflammatory cascade, immunostimulation, and gene therapy. Omalizumab, a humanized anti IgE monoclonal antibody, is expected to be marketed soon in the Netherlands. At present, these kinds of relatively expensive and demanding treatment modalities will have to be reserved for patients that cannot be controlled adequately with regular therapy. Gene therapy may offer unique oppurtunities for treating **asthma** in the future, but for now it is still far from application in human **asthma**.

L7 ANSWER 22 OF 46 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2002:233192 SCISEARCH
THE GENUINE ARTICLE: 528XX
TITLE: Interleukin-4 and **interleukin-5** gene expression and inflammation in the mucus-secreting glands and subepithelial tissue of smokers with chronic bronchitis - Lack of relationship with CD8(+) cells
AUTHOR: Zhu J; Majumdar S; Qiu Y; Ansari T; Oliva A; Kips J C; Pauwels R A; De Rose V; Jeffery P K (Reprint)
CORPORATE SOURCE: Royal Brompton Hosp, Lung Pathol Unit, Sydney St, London SW3 6NP, England (Reprint); Univ London Imperial Coll Sci Technol & Med, Sch Med, Dept Gene Therapy, London, England; Univ Turin, Dept Clin & Biol Sci, Turin, Italy; Univ Hosp, Dept Pathol, Ghent, Belgium
COUNTRY OF AUTHOR: England; Italy; Belgium
SOURCE: AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, (15 DEC 2001) Vol. 164, No. 12, pp. 2220-2228.
Publisher: AMER THORACIC SOC, 1740 BROADWAY, NEW YORK, NY 10019-4374 USA.
ISSN: 1073-449X.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 43

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We wished to determine if the inflammatory cells surrounding the airway mucus-secreting glands in chronic bronchitis (CB) were associated with interleukin (IL)-4 and **IL-5** mRNA expression and whether the CD8 T cell population expressed these cytokines. Digoxigenin-labeled IL-4 and **IL-5 antisense**

RNA probes were used to detect gene expression in 11 asymptomic smokers (AS), 11 smokers with CB alone with normal lung function, and 10 smokers with chronic bronchitis and coexisting chronic obstructive pulmonary disease (CB+COPD; FEV1% of predicted of 43-77% and FEV1/ FVC of 51-68%). There were approximately three times as many IL-4 than **IL-5** mRNA(+) cells. The highest number of IL-4 mRNA(+) cells were in the submucosal glands of the CB group with normal lung function (216/mm(2)), significantly higher than the values in either the AS (63/mm(2)) or the CB+COPD (87/mm(2)) groups, respectively ($p < 0.01$). There were similar group differences when the total numbers of inflammatory cells were compared. Accordingly, there was a positive correlation between the number of IL-4 mRNA(+) cells and the total number of inflammatory cells in both the subepithelium and glandular compartments ($r = 0.60$; $p = 0.01$ and $r = 0.70$; $p = 0.02$, respectively). There were no significant associations between the numbers of CD8(+) and IL-4 or **IL-5** mRNA+ cells. Of 1328 IL-4(+) and 1404 CD8+ cells counted none was double labeled. Of 727 **IL-5**(+) and 1569 CD8(+) cells, none was double labeled. In contrast, as a positive control, 34% of tumor necrosis factor (TNF)-alpha(+) cells were also CD8(+) and 15% of CD8(+) cells were TNF-alpha positive. Thus, cells other than the CD8(+) phenotype produce IL-4 and **IL-5** in CB. We conclude that there is increased inflammation and IL-4 gene expression in the mucus-secreting glands and the airway mucosa of smokers with bronchitis: both are lower in those with CB and coexisting COPD suggesting that airway inflammation in CB is reduced when airway obstruction develops.

L7 ANSWER 23 OF 46 MEDLINE on STN
ACCESSION NUMBER: 2001678769 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11724761
TITLE: **Interleukin-5** in growth and differentiation of blood eosinophil progenitors in **asthma**: effect of glucocorticoids.
AUTHOR: Kuo H P; Wang C H; Lin H C; Hwang K S; Liu S L; Chung K F
CORPORATE SOURCE: Department of Thoracic Medicine, Chang Gung Memorial Hospital, Taipei, Taiwan.
SOURCE: British journal of pharmacology, (2001 Dec) 134 (7) 1539-47.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20011129
Last Updated on STN: 20020125
Entered Medline: 20020114

AB 1. There are increased numbers of circulating CD34(+) progenitor cells for eosinophils in patients with atopic **asthma**, with a further increase following allergen exposure or spontaneous worsening of **asthma**. We investigated the expression of **IL-5** and IL-5Ralpha receptor in circulating CD34(+) progenitor cells in allergic asthmatics and the effects of corticosteroids. 2. Using double-staining techniques, up to 50% of CD34(+) cells expressed intracellular **IL-5**, and by RT - PCR, there was significant expression of **IL-5** mRNA. When cultured in a semi-liquid methylcellulose medium, there were more eosinophil colony-forming units grown from asthmatic non-adherent mononuclear cell depleted of T cells in the presence of the growth factors GM-CSF, SCF and IL-3, but not of **IL-5**. 3. An anti-IL-5Ralpha receptor antibody and an anti-sense **IL-5** oligonucleotide reduced the number of eosinophil colony forming units. No **IL-**

5 mRNA or protein expression on T cells was observed in asthmatics or normal subjects. In the presence of growth factors including **IL-5**, there were significantly greater colony numbers with eosinophilic lineage grown from either asthmatics or normal subjects. 4. Dexamethasone (10(-6) M) suppressed **IL-5** mRNA and protein expression in CD34(+) cells, and reduced eosinophil colony-forming units in asthmatics, but not in normal subjects. Dexamethasone did not change the expression of IL-5Ralpha on CD34(+) cells. 5. We conclude that there is increased expression of **IL-5** on blood CD34(+) cells of patients with **asthma** and that this expression may auto-regulate eosinophilic colony formation from these progenitor cells. Corticosteroids inhibit the expression of **IL-5** in circulating CD34(+) progenitor cells.

L7 ANSWER 24 OF 46 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001242454 EMBASE
TITLE: Cytokine therapeutics for **asthma**: An appraisal of current evidence and future prospects.
AUTHOR: Alvarez D.; Wiley R.E.; Jordana M.
CORPORATE SOURCE: M. Jordana, Dept. of Pathol./Molecular Medicine, Division of Respiratory Dis./Allergy, McMaster University, 1200 Main Street West, Hamilton, Ont. L8N 3Z5, Canada. jordanam@mcmaster.ca
SOURCE: Current Pharmaceutical Design, (2001) 7/11 (1059-1081). Refs: 204
ISSN: 1381-6128 CODEN: CPDEFP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Although current pharmacopoeia is effective in alleviating **asthma** symptomatology, it is equally unable to modify the fundamental immunological basis of the allergic diathesis. The explosion in knowledge of the immunobiology of cytokines that has occurred in the last decade has remarkably clarified our understanding of the pathogenesis of allergic **asthma**, and has unleashed a plethora of compelling opportunities. In the first part of this review, we will summarize current knowledge on the pathogenesis of allergic **asthma**, with particular emphasis on relevant cytokine networks. This will position us to appraise critically initiatives in the search to modulate cytokine targets that are key to the expression of the allergic **asthma** phenotype. We will review the use of recombinant cytokines, soluble cytokine receptors, cytokine receptor antagonists and cytokine inhibitors, in pre-clinical and clinical development. Finally, we will assess the applicability of transgene-based modalities, including anti-sense oligonucleotide technology and gene therapy, as novel therapeutic strategies in the treatment of allergic **asthma**.

L7 ANSWER 25 OF 46 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2001:526144 SCISEARCH
THE GENUINE ARTICLE: 445JR
TITLE: Grass pollen immunotherapy: Symptomatic improvement correlates with reductions in eosinophils and **IL-5** mRNA expression in the nasal mucosa during the pollen season
AUTHOR: Wilson D R; Nouri-Aria K T; Walker S M; Pajno G B; O'Brien F; Jacobson M R; Mackay I S; Durham S R (Reprint)

CORPORATE SOURCE: Natl Heart & Lung Inst, Imperial Coll, Sch Med, Dept Upper Resp Med, Dovehouse St, London SW3 6LY, England (Reprint); Natl Heart & Lung Inst, Imperial Coll, Sch Med, Dept Upper Resp Med, London SW3 6LY, England
COUNTRY OF AUTHOR: England
SOURCE: JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, (JUN 2001) Vol. 107, No. 6, pp. 971-976.
Publisher: MOSBY, INC, 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318 USA.
ISSN: 0091-6749.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 41

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: Tissue eosinophilia and infiltration by T(H)2-type T tells are characteristic features of allergic rhinitis both after allergen challenge and during natural allergen exposure. Specific immunotherapy inhibits allergen-induced nasal eosinophilia.

Objectives: We sought to assess, in the context of a randomized trial, the relationships between symptomatic improvement after immunotherapy and eosinophil numbers and **IL-5** expression in the nasal mucosa during the pollen season. Methods: Nasal biopsy specimens were taken from 37 adults with severe summer hay fever at baseline (out of season) and at peak season after 2 years of treatment with a depot grass pollen extract or placebo. Biopsy specimens were processed for immunohistochemistry by using mAbs against eosinophils (EG2), T cells (CD3), and IL-2 receptor-positive cells (CD25), as well as for in situ hybridization by using a sulfur 35-labeled **antisense** riboprobe directed against **IL-5**.

Results: Immunotherapy significantly reduced symptoms (49%, P = .01) and medication requirements (80%, P = .007) compared with placebo. There was a 400% increase (P = .004) in eosinophils during the pollen season in placebo-treated patients, which was inhibited in the immunotherapy group (20% increase, P = .04 between groups). Seasonal increases were also observed for CD25(+) cells (P = .002), CD3(+) cells (P = .02), and **IL-5** mRNA-expressing cells (P = .03) in the placebo group but not in the immunotherapy group. A significant correlation was observed between eosinophils and **IL-5** expression (r = 0.5, P < .05). Both eosinophils (r = 0.6, P < .02) and **IL-5** (r = 0.6, P < .02) correlated with symptoms after immunotherapy. Conclusion: Improvement in symptoms after grass pollen immunotherapy may result, at least in part, from inhibition of **IL-5** -dependent tissue eosinophilia during the pollen season.

Conclusion: Improvement in symptoms after grass pollen immunotherapy may result, at least in part, from inhibition of **IL-5** -dependent tissue eosinophilia during the pollen season.

L7 ANSWER 26 OF 46 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2001681753 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11727517
TITLE: **Interleukin-5**: a novel target for **asthma** therapy.
AUTHOR: Blumchen K; Kallínich T; Hamelmann E
CORPORATE SOURCE: Department of Paediatrics, Pulmonology and Immunology, Charite'-Campus-Virchow-Klinikum, Berlin, Germany.
SOURCE: Expert opinion on biological therapy, (2001 May) 1 (3) 433-53. Ref: 171
Journal code: 101125414. ISSN: 1471-2598.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011203
Last Updated on STN: 20021008
Entered Medline: 20011220

AB Eosinophilic airway inflammation is the main histologic correlate of airway hyper-responsiveness (AHR) and tissue injury in the pathogenesis of bronchial **asthma**. There is strong evidence for a central role of CD4+ T-cells secreting pro-allergic Th2-cytokines, such as IL-4 and **IL-5**, in the induction of airway eosinophilia and AHR. **IL-5** appears to be one of the main pro-inflammatory mediators among a growing number of cytokines and chemokines that induce, regulate and sustain eosinophilic airway inflammation. Animal studies provide confirmatory evidence for the important role of **IL-5** in the induction and maintenance of eosinophilic airway infiltration leading to altered airway function. Interfering with the action of **IL-5** represents one of the new immunomodulatory therapeutic strategies in the treatment of bronchial **asthma**. Compared to established immunosuppressive agents like steroids, a major advantage of this strategy is the specificity of reducing eosinophilic inflammation, thus possibly acting nearly without side effects. There are several possible ways to inhibit the effects of **IL-5** including alteration of the signalling pathway in the **IL-5** producing cell by inhibition or modification of transcription factors or the use of **antisense** oligonucleotides and blocking of the **IL-5** protein itself by monoclonal antibodies, soluble **IL-5** receptor or antagonists of the **IL-5** receptor expressed on the surface of eosinophils. Although preliminary data from the first clinical trials gave rise to skepticism about the efficacy of anti-**IL-5** treatment regarding the improvement of lung function of asthmatic patients, further studies with a better defined profile of the target population may provide encouraging results, allowing the introduction of this truly new therapeutic concept.

L7 ANSWER 27 OF 46 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 9

ACCESSION NUMBER: 2001:152779 BIOSIS
DOCUMENT NUMBER: PREV200100152779
TITLE: In vitro and in vivo inhibition of interleukin (**IL**)-**5**-mediated eosinopoiesis by murine IL-5Ralpha **antisense** oligonucleotide.
AUTHOR(S): Lach-Trifilieff, Estelle; McKay, Robert A.; Monia, Brett P.; Karras, James G.; Walker, Christoph [Reprint author]
CORPORATE SOURCE: Novartis Horsham Research Centre, Wimblehurst Road, Horsham, RH12 5AB, UK
christoph.walker@pharma.novartis.com
SOURCE: American Journal of Respiratory Cell and Molecular Biology, (February, 2001) Vol. 24, No. 2, pp. 116-122. print.
CODEN: AJRBEL. ISSN: 1044-1549.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Mar 2001
Last Updated on STN: 15 Feb 2002

AB The unique role of interleukin (**IL**)-**5** in eosinophil production, activation, and localization makes this cytokine a prime target for therapeutic intervention in diseases characterized by a selective blood and tissue eosinophilia. In an attempt to block the effects of **IL-5** on eosinophils, a strategy was developed to suppress the expression of the **IL-5** receptor alpha chain (IL-5Ralpha) by **antisense** oligonucleotides

(ASOs). IL-5Ralpha ASOs were identified which selectively and specifically suppress the expression of messenger RNA and proteins of both the membrane and the soluble form of the receptor in constitutively IL-5R-expressing murine BCL-1 cells in vitro. Moreover, these IL-5Ralpha-specific ASOs were able to selectively inhibit the **IL-5**-induced eosinopoesis from murine fetal liver and bone marrow cells in vitro, suggesting that these molecules may affect the development of **IL-5**-mediated eosinophilia in vivo. Indeed, intravenous administration of IL-5Ralpha-specific ASOs not only suppressed the bone-marrow and blood eosinophilia in mice after short-term treatment with recombinant murine **IL-5** but also inhibited the development of blood and tissue eosinophilia in a ragweed-induced allergic peritonitis model. Thus, blocking the expression of IL-5Ralpha on eosinophil using ASOs may have therapeutic benefits in eosinophilic diseases such as **asthma**.

L7 ANSWER 28 OF 46 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 2000261683 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10799906
TITLE: Inhibition of antigen-induced eosinophilia and late phase **airway hyperresponsiveness** by an **IL-5 antisense** oligonucleotide in mouse models of **asthma**.
AUTHOR: Karras J G; McGraw K; McKay R A; Cooper S R; Lerner D; Lu T; Walker C; Dean N M; Monia B P
CORPORATE SOURCE: Departments of Molecular and Cellular Pharmacology and Pharmacology, Isis Pharmaceuticals, Carlsbad, CA 92008, USA.. jkarras@isisph.com
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (2000 May 15) 164 (10) 5409-15.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000616
Last Updated on STN: 20000616
Entered Medline: 20000607

AB Chronic airway eosinophilia is associated with allergic **asthma** and is mediated in part by secretion of **IL-5** from allergen-specific Th2 lymphocytes. **IL-5** is a known maturation and antiapoptotic factor for eosinophils and stimulates release of nascent eosinophils from bone marrow into the peripheral circulation. An **antisense** oligonucleotide found to specifically inhibit **IL-5** expression in vitro was observed to significantly reduce experimentally induced eosinophilia in vivo, in both the murine OVA lung challenge and allergic peritonitis models. Intravenous administration resulted in sequence-dependent inhibition of eosinophilia coincident with reduction of **IL-5** protein levels, supporting an **antisense** mechanism of action. Potent suppression of lung eosinophilia was observed up to 17 days after cessation of oligonucleotide dosing, indicating achievement of prolonged protection with this strategy. Furthermore, sequence-specific, **antisense** oligonucleotide-mediated inhibition of Ag-mediated late phase **airway hyperresponsiveness** was also observed. These data underscore the potential utility of an **antisense** approach targeting **IL-5** for the treatment of **asthma** and eosinophilic diseases.

L7 ANSWER 29 OF 46 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2000:632604 SCISEARCH
THE GENUINE ARTICLE: 344VN
TITLE: **IL-5**: biology and potential therapeutic applications
AUTHOR: Weltman J K (Reprint); Karim A S
CORPORATE SOURCE: BROWN UNIV, SCH MED, DEPT MED, PROVIDENCE, RI 02912 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: EXPERT OPINION ON INVESTIGATIONAL DRUGS, (MAR 2000) Vol. 9, No. 3, pp. 491-496.
Publisher: ASHLEY PUBL LTD, 1ST FL, THE LIBRARY, 1 SHEPHERDS HILL HIGHGATE, LONDON N6 5QJ, ENGLAND.
ISSN: 1354-3784.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 54

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **IL-5** is the predominant cytokine associated with antigen-induced eosinophilic inflammation in the lung. The activation of Th-2 cells leads to the production of **IL-5**. The pro-eosinophilic effects of **IL-5** include: (1) enhanced replication and differentiation of eosinophilic myelocytes; (2) enhanced degranulation of eosinophils; (3) prolonged survival time of eosinophils: and (4) enhanced adhesion of eosinophils. The effects of **IL-5** are mediated via the interaction of **IL-5** with receptors (IL-5R) that are expressed on the eosinophil cell membrane. Intracellular signalling produced by occupation of the IL-5R by **IL-5** occurs via the JAK-STAT system. **IL-5** is a 45kDa glycoprotein consisting of mio identical polypeptide. chains. The 5'-promoter region of the **IL-5** gene contains elements that are down-regulated by glucocorticoids. Anti-**IL-5** reagents have the potential to suppress **IL-5** activity without the side effects of glucocorticoids. Studies using monoclonal antibodies (mAbs) against **IL-5** have established the feasibility of suppressing eosinophilic inflammation by specifically blocking **IL-5** activity. Studies with **antisense** **IL-5** are beginning to provide the basis for non-glucocorticoid, sequence-specific oligonucleotide inhibitors of **IL-5**. Research has begun on the development of mAbs and **antisense** oligonucleotide inhibitors of **IL-5** that can be inhaled and applied topically.

L7 ANSWER 30 OF 46 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2001:122585 BIOSIS
DOCUMENT NUMBER: PREV200100122585
TITLE: Experimental study on treatment of bronchial **asthma** with **antisense** oligonucleotid.
AUTHOR(S): Wang Mei-qin [Reprint author]; Bai Chun-xue [Reprint author]; Niu Shan-fu [Reprint author]; Fang Xiao-hui [Reprint author]; Chen Chang-qing; Chen Bo
CORPORATE SOURCE: Institute of Respiratory Disease, Zhongshan Hospital, Shanghai Medical University, Shanghai, 200032, China
SOURCE: Journal of Shanghai Medical University, (Nov., 2000) Vol. 27, No. 6, pp. 464-467, 470. print.
CODEN: SYDXEE. ISSN: 0257-8131.
DOCUMENT TYPE: Article
LANGUAGE: Chinese
ENTRY DATE: Entered STN: 7 Mar 2001
Last Updated on STN: 15 Feb 2002

AB Purpose To explore the possibility and the effect of therapeutic bronchial

asthma by **antisense** oligonucleotid. Methods Based on the **IL-5** cDNA sequence of mouse, a segment of **antisense** oligonucleotid was designed and synthetized. 5'-labeling of **antisense** oligonucleotid was signed by T4 PNK in order that the efficiency of stearylamine liposome in transfe-ting **antisense** oligonucleotid can be evaluated. Astham model was duplicated with ovalbumin (OVA) absorbed to aluminum hydroxide. T lymphocytes of mice were separated by nylon fiber method, then T lymphocytes transfected a different content of **antisense** oligonucleotid with stearylamine phys. positive liposome were cultured respectively in order to observe the effect of **antisense** oligonucleotid on **IL-5** produced by T lymphocytes. **IL-5** levels in the supernatants of T lymphocytes culture were determined by ELISA. Results Stearylamine liposome could markedly increase the efficiency of **antisense** oligonucleotid transfection. The efficiency of **antisense** oligonucleotid transfection was the best at 1:15 m/m (**antisense** oligonucleotid and SA liposome) and it was increased approximately 12 times. In healthy and **asthma** Balb/c mice, **IL-5** was not detected in the supernatants of T lymphocytes culture without challenge with OVA. However, **IL-5** was increased markedly in the supernatants of T lymphocytes culture challenged with OVA. After transfecting a different concentration **antisense** oligonucleotid, **IL-5** levels in the supernatants of T lymphocytes culture were significantly lower than those in control cells without **antisense** oligonucleotide transfection. **IL-5** levels decreased from (44.60 +- 6.23) to (30.70 +- 7.362), (17.20 +- 6.181) and (8.16 +- 2.34) pg/ml respectively. And **IL-5** synthesis was inhibited by 31.17%, 61.43% and 81.7% respectively. Conclusions **IL-5** synthesis could be obviously inhibited by **antisense** oligonucleotid and showed a markedly relation between quantitative and effect. It is supported that the production of **IL-5** be inhibited through preventing the transcription of **IL-5** from T lymphocytes. The study provides foundation for **antisense** gene therapeutic **asthma**.

L7 ANSWER 31 OF 46 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001009738 EMBASE
TITLE: **Interleukin-5**: A drug target for allergic diseases.
AUTHOR: Sanderson C.J.; Urwin D.
CORPORATE SOURCE: C.J. Sanderson, Dept. of Molecular Immunology, Western Australian Inst. Med. Res., Curtin University of Technology, Rear 50 Murray Street, Perth 6000, WA, Australia. colin@cyllene.uwa.edu.au
SOURCE: Current Opinion in Investigational Drugs, (2000) 1/4 (435-441).
Refs: 54
ISSN: 0967-8298 CODEN: CIDREE
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 026 Immunology, Serology and Transplantation
015 Chest Diseases, Thoracic Surgery and Tuberculosis
005 General Pathology and Pathological Anatomy
037 Drug Literature Index
030 Pharmacology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB There is a large body of evidence that eosinophils are a key component of the allergic response in **asthma**. Interleukin (**IL**) **5** is uniquely involved in the production of eosinophils, and with

a variety of other cytokines and factors controls their activation, localization and survival. Thus, **IL-5** is an important drug target for new anti-asthmatics. The routes to drug discovery are based on screens for inhibitors of **IL-5** production, ligand antagonists, control of receptor expression and receptor activation. In this review, we will discuss specific targets and screening assays with examples of some of the compounds in development.

L7 ANSWER 32 OF 46 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 11

ACCESSION NUMBER: 2000:398525 BIOSIS
DOCUMENT NUMBER: PREV200000398525
TITLE: Deletion of individual exons and induction of soluble murine **interleukin-5** receptor-alpha chain expression through **antisense** oligonucleotide-mediated redirection of pre-mRNA splicing.
AUTHOR(S): Karras, James G. [Reprint author]; McKay, Robert A.; Dean, Nicholas M.; Monia, Brett P.
CORPORATE SOURCE: Department of Molecular and Cellular Pharmacology, Isis Pharmaceuticals, 2292 Faraday Ave., Carlsbad, CA, 92008, USA
SOURCE: Molecular Pharmacology, (August, 2000) Vol. 58, No. 2, pp. 380-387. print.
CODEN: MOPMA3. ISSN: 0026-895X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Sep 2000
Last Updated on STN: 8 Jan 2002

AB Expression of the **interleukin-5** receptor-alpha (IL-5Ralpha) chain is thought to play an important role in the pathogenesis of **asthma** and other eosinophilic diseases. With **antisense** oligonucleotides (ASOs) chemically modified to provide increased hybridization affinity for RNA but that do not support RNase H-mediated cleavage (2'-O-methoxyethyl-modified ASOs), we show that constitutive splicing of murine IL-5Ralpha mRNA can be modulated in cells such that individual exons may be selectively deleted from mature transcripts. Specific deletion of individual exons and redirection of alternative splicing of the IL-5Ralpha mRNA have been achieved with this approach, by targeting 3'-splice sites or exon sequences immediately downstream of an alternative splice site. ASO targeting with these strategies resulted in inhibition of mRNA and protein levels of the membrane IL-5Ralpha isoform capable of signaling **IL-5** -mediated growth and antiapoptotic signals to eosinophils. Membrane isoform IL-5Ralpha inhibition was coupled with an increase in expression of mRNA for the alternatively spliced soluble isoform, which binds **IL-5** extracellularly and may block its function. These observations suggest the potential general therapeutic use of an **antisense** approach to increase expression of variant RNA transcripts and to thereby produce proteins devoid of specific functional domains that may impact disease processes, as well as its specific utility for modulating expression of a key cytokine receptor implicated in allergic inflammation.

L7 ANSWER 33 OF 46 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 12

ACCESSION NUMBER: 2001:812 BIOSIS
DOCUMENT NUMBER: PREV200100000812
TITLE: **Antisense** inhibition of membrane-bound human **interleukin-5** receptor-alpha chain does not affect soluble receptor expression and induces apoptosis in TF-1 cells.
AUTHOR(S): Karras, James G. [Reprint author]; McKay, Robert A.; Lu,

Tao; Dean, Nicholas M.; Monia, Brett P.
CORPORATE SOURCE: Department of Molecular and Cellular Pharmacology, ISIS Pharmaceuticals, 2292 Faraday Avenue, Carlsbad, CA, 92008, USA
SOURCE: Antisense and Nucleic Acid Drug Development, (October, 2000) Vol. 10, No. 5, pp. 347-357. print.
ISSN: 1087-2906.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Dec 2000
Last Updated on STN: 21 Dec 2000

AB Binding of human **interleukin-5** (HuIL-5) to its membrane-anchored receptor (IL-5R) triggers multiple signaling pathways, cellular proliferation, and maturational responses, as well as protection from apoptosis. In contrast, soluble forms of the HuIL-5R have been shown to inhibit **IL-5** signaling and, therefore, may represent naturally occurring negative regulators of **IL-5** function. Because of the central role of **IL-5** in promoting eosinophilia and **airway hyperresponsiveness** in animal models of **asthma**, **antisense** oligonucleotides specific either for the membrane form alone or for sequences shared between both the membrane and soluble forms of the HuIL-5Ralpha ligand binding chain were designed. The activities of these oligonucleotides were characterized in IL-5R-expressing erythroleukemic TF-1 cells. Herein we report that an **antisense** oligonucleotide targeted to a sequence unique to the alternatively spliced membrane-bound form of the HuIL-5Ralpha chain has been developed that selectively inhibits membrane, but not soluble, mRNA isoform expression. Both this membrane-specific oligonucleotide and an **antisense** oligonucleotide targeted to sequence common to both membrane and soluble isoforms were found to potently suppress cell surface IL-5Ralpha levels and **IL-5**-mediated cell survival by inducing apoptosis similar to **IL-5** withdrawal. Thus, these oligonucleotides represent unique genetic agents with therapeutic potential for diseases with an eosinophilic component.

L7 ANSWER 34 OF 46 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2000038635 EMBASE
TITLE: Prospects for a vaccine in allergic diseases and **asthma**.
AUTHOR: Bousquet J.; Yssel H.; Demoly P.
CORPORATE SOURCE: Prof. J. Bousquet, Service des Maladies Respiratoires, Hopital Arnaud de Villeneuve, 34295 Montpellier Cedex 5, France. bousquet@montp.inserm.fr
SOURCE: BioDrugs, (2000) 13/1 (61-75).
Refs: 137
ISSN: 1173-8804 CODEN: BIDRF4
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Allergen-specific immunotherapy is widely used to treat allergic diseases, and current research is now focusing on the development of therapeutic vaccines acting on the IgE immune response following allergen challenge. The IgE immune response is dependent on genetic and environmental factors; production of IgE results from complex interactions among B cells, T cells, mast cells, basophils, surface and adhesion molecules and various cytokines. New vaccination methods under investigation involve allergen-

specific or nonspecific methodology. Allergen-specific methods currently being developed include allergoids, passive saturation of effector cells, plasmid DNA immunisation and antigen-antibody complexes. The mechanisms of immunotherapy using allergen-specific methods differ with the allergens and the route of immunisation used (parenteral, intranasal, sublingual, oral or bronchial). Many vaccines being developed at present comprise synthetic, recombinant or highly purified subunit antigens, which although they have increased safety may also be less immunogenic. It is hoped that the addition of adjuvants will overcome this drawback. Methods of increasing the dose of allergen while reducing the possibility of an anaphylactic reaction include the use of non-anaphylactic isoforms of the allergens, alteration of the tertiary structure of the allergens and construction of minimal allergen- derived T cell peptides. Nonspecific approaches include humanised anti-IgE antibodies, moderation of the T(H)2 cytokine network and **antisense** oligodeoxynucleotide therapy.

L7 ANSWER 35 OF 46 MEDLINE on STN
ACCESSION NUMBER: 1999323991 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10395690
TITLE: A novel Lyn-binding peptide inhibitor blocks eosinophil differentiation, survival, and airway eosinophilic inflammation.
AUTHOR: Adachi T; Stafford S; Sur S; Alam R
CORPORATE SOURCE: Department of Internal Medicine, Division of Allergy and Immunology, University of Texas Medical Branch, Galveston 77555, USA.
CONTRACT NUMBER: AI135713 (NIAID)
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (1999 Jul. 15) 163 (2) 939-46.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990806
Last Updated on STN: 20000303
Entered Medline: 19990729

AB Receptor antagonists block all receptor-coupled signaling pathways indiscriminately. We introduce a novel class of peptide inhibitors that is designed to block a specific signal from a receptor while keeping other signals intact. This concept was tested in the model of **IL-5** signaling via Lyn kinase. We have previously mapped the Lyn-binding site of the **IL-5**/GM-CSF receptor common beta (beta c) subunit. In the present study, we designed a peptide inhibitor using the Lyn-binding sequence. The peptide was N-stearated to enable cellular internalization. The stearated peptide blocked the binding of Lyn to the beta c receptor and the activation of Lyn. The lipopeptide did not affect the activation of Janus kinase 2 or its association with beta c. The inhibitor blocked the Lyn-dependent functions of **IL-5** in vitro (e.g., eosinophil differentiation from stem cells and eosinophil survival). It did not affect eosinophil degranulation. When applied in vivo, the Lyn-binding peptide significantly inhibited airway eosinophil influx in a mouse model of **asthma**. The lipopeptide had no effect on basophil histamine release or on the proliferation of B cells and T cells. To our knowledge, this is the first report on an inhibitor of **IL-5** that blocks eosinophil differentiation, survival, and airway eosinophilic inflammation. This novel strategy to develop peptide inhibitors can be applied to other receptors.

L7 ANSWER 36 OF 46 EMBASE

on STN
ACCESSION NUMBER: 1999378990 EMBASE
TITLE: Respirable **antisense** oligonucleotide (RASON) therapy for allergic **asthma**.
AUTHOR: Metzger W.J.; Nyce J.W.
CORPORATE SOURCE: Dr. W.J. Metzger, East Carolina University, School of Medicine, Sec. of Allergy, Asthma/Immunology, Greenville, NC 27858, United States
SOURCE: BioDrugs, (1999) 12/4 (237-243).
Refs: 37
ISSN: 1173-8804 CODEN: BIDRF4
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB A new technology for treating respiratory disease, respirable **antisense** oligonucleotides (RASONs), has recently been developed by our group. RASONs are short, single-stranded nucleic acids, generally modified to reduce degradation. They differ from traditional drugs, which usually antagonise preformed proteins already functioning in a disease process. Instead, RASONs can attenuate the expression of disease-associated genes by targeting the messenger RNA (mRNA). Delivered directly to the target tissue, the lung, they avoid the problems of ineffective delivery encountered by other routes of administration. When an adenosine A1 **antisense** oligonucleotide was delivered to the lungs of allergic rabbits with up-regulated A1 adenosine receptors, desensitisation to the bronchoconstrictor effects of adenosine, histamine and a common aeroallergen (dust mite) occurred. The effect on A1 receptors persisted on average for nearly 7 days. RASON (the phosphorothioate **antisense** oligonucleotide EPI-2010) administered in low dosage was evenly distributed throughout the lung (with no detectable systemic active metabolites), and was excreter primarily in urine. These results demonstrate that RASONs can be efficiently and effectively delivered to the peripheral lung. They potently and selectively attenuate the expression of disease-associated genes, an approach to therapy which is now being extended to other potentially important mediators of bronchial **asthma**.

L7 ANSWER 37 OF 46 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 13
ACCESSION NUMBER: 1999:417007 BIOSIS
DOCUMENT NUMBER: PREV199900417007
TITLE: Adoptively transferred late allergic response is inhibited by IL-4, but not **IL-5**, **antisense** oligonucleotide.
AUTHOR(S): Molet, Sophie; Ramos-Barbon, David; Martin, James G.; Hamid, Qutayba [Reprint author]
CORPORATE SOURCE: Meakins-Christie Laboratories, McGill University, 3626 St Urbain, Montreal, PQ, H2X 2P2, Canada
SOURCE: Journal of Allergy and Clinical Immunology, (July, 1999) Vol. 104, No. 1, pp. 205-214. print.
CODEN: JACIBY. ISSN: 0091-6749.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 18 Oct 1999
Last Updated on STN: 18 Oct 1999

AB Background: We have shown previously that the late airways response (LAR) can be transferred by ovalbumin-primed CD4+ T lymphocytes in Brown Norway

rats. This response is associated with an increase of eosinophils and high expression of TH2 cytokines (IL-4 and **IL-5**) in bronchoalveolar lavage (BAL) fluid. Objective: In this study we hypothesized that the inhibition of IL-4 or **IL-5** production in the CD4+ cells transferred to a naive animal could decrease the LAR and prevent airway eosinophilia in response to antigen challenge. Methods: CD4+ cells, purified from the cervical lymph nodes of ovalbumin-sensitized rats, were maintained in culture for 6 hours with medium alone or with 10 mug/mL IL-4 **antisense** (AS), **IL -5** AS, or control AS oligodeoxynucleotide. Then the cells were administrated intraperitoneally to naive rats, which were challenged 2 days later by a 5 % ovalbumin aerosol. The lung resistance was measured for 8 hours, and then BAL was performed. Cytospin preparations from BAL cells were assessed for the presence of eosinophils by immunocytochemistry for major basic protein and for IL-4, **IL-5**, and IFN-gamma expression. Results: In rats injected with IL-4 AS-treated T cells, LAR, eosinophils, and IL-4 and **IL-5** expression were significantly decreased compared with the other groups. Only **IL-5** expression in BAL fluid was slightly decreased consequent to the transfer of **IL-5** AS-treated T cells. Conclusion: This study demonstrates that, in the CD4+ T cell-driven LAR, the early production of IL-4, but not **IL-5**, by the transferred CD4+ cells is essential for the development of the LAR.

L7 ANSWER 38 OF 46 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 1998451425 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9780145
TITLE: Differential responsiveness of the **IL-5** and IL-4 genes to transcription factor GATA-3.
AUTHOR: Zhang D H; Yang L; Ray A
CORPORATE SOURCE: Department of Internal Medicine, Yale University School of Medicine, New Haven, CT 06520, USA.
CONTRACT NUMBER: P50 HL56389 (NHLBI)
R01 AI31137 (NIAID)
R01 HL 56843 (NHLBI)
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (1998 Oct 15) 161 (8) 3817-21.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; AIDS
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981104

AB The cytokines IL-4 and **IL-5** are often coordinately produced by Th2 cells as in **asthma**. However, it is unclear whether similar molecular mechanisms underlie transcription of the two genes. We have previously shown that the transcription factor GATA-3 is expressed in Th2 but not Th1 cells and is crucial for activation of the **IL-5** promoter by different stimuli. In a different study, GATA-3 was shown to be sufficient for the expression of IL-4 and other Th2 cytokine genes. Here, we show that ectopic expression of GATA-3 is sufficient to drive **IL-5** but not IL-4 gene expression. Also, in Th2 cells, **antisense** GATA-3 RNA inhibits **IL-5** but not IL-4 promoter activation. The induction of **IL-5** gene expression by GATA-3 involves high affinity binding of GATA-3 to an inverted GATA repeat in the **IL-5** promoter.

L7 ANSWER 39 OF 46 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation.

on STN
ACCESSION NUMBER: 1999:38326 SCISEARCH
THE GENUINE ARTICLE: 151GJ
TITLE: Corticosteroid-resistant bronchial **asthma** is associated with increased c-fos expression in monocytes and T lymphocytes
AUTHOR: Lane S J; Adcock I M; Richards D; Hawrylowicz C; Barnes P J; Lee T H (Reprint)
CORPORATE SOURCE: GUYS HOSP, DEPT RESP MED & ALLERGY, 5TH FLOOR, THOMAS GUY HOUSE, LONDON SE1 9RT, ENGLAND (Reprint); GUYS HOSP, DEPT RESP MED & ALLERGY, LONDON SE1 9RT, ENGLAND; NATL HEART & LUNG INST, DEPT THORAC MED, LONDON SW3 6LY, ENGLAND
COUNTRY OF AUTHOR: ENGLAND
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (15 DEC 1998) Vol. 102, No. 12, pp. 2156-2164.
Publisher: ROCKEFELLER UNIV PRESS, 1114 FIRST AVE, 4TH FL, NEW YORK, NY 10021.
ISSN: 0021-9738.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 34

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Unstimulated peripheral blood mononuclear cells (PBMCs) from corticosteroid-resistant (CR) but not corticosteroid-sensitive (CS) asthmatics demonstrate increased activating peptide-1 (AP-1)- and decreased glucocorticoid receptor (GR)-DNA binding, We test whether these abnormalities are associated with excessive generation of c-fos, the inducible component of AP-1., The c-fos transcription rate, mRNA and protein levels, and GR-DNA binding were quantitated in PBMCs, T cells, and monocytes from CS, CR, and nonasthmatic subjects. There was a 1.7-, 4.2-, and 2.3-fold greater increase in the baseline c-fos transcription rate, mRNA expression, and protein levels, respectively, in PBMCs derived from CR compared with CS patients. At optimal stimulation with PMA, there was a 5.7-, 3.4-, and 2-fold greater increase in the c-fos transcription rate, mRNA accumulation, and protein levels, respectively, in CR compared with CS PBMCs. These abnormalities were detected in both the T cell and monocyte subpopulations. PMA stimulation converted PBMCs from a CS to a CR phenotype and was associated with direct interaction between c-Fos and the GR, Pretreatment of PBMCs from CR patients with c-fos **antisense** oligonucleotides enhanced GR-DNA binding activity in CR PBMCs stimulated with dexamethasone, We suggest that increased c-fos synthesis provides a major mechanism for the increased AP-1- and decreased GR-DNA binding seen in CR **asthma**.

L7 ANSWER 40 OF 46 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1998:331776 BIOSIS
DOCUMENT NUMBER: PREV199800331776
TITLE: Selection of **antisense** sequences against human **interleukin-5** by maximization of G plus C content.
AUTHOR(S): Weltman, Joel K.; Karim, Aftab S.
CORPORATE SOURCE: Dep. Med., Brown Univ. Med., Providence, RI 02912, USA
SOURCE: FASEB Journal, (April 24, 1998) Vol. 12, No. 8, pp. A1465. print.
Meeting Info.: Meeting of the American Society for Biochemistry and Molecular Biology. Washington, D.C., USA. May 16-20, 1998. American Society for Biochemistry and Molecular Biology.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)

Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Aug 1998
Last Updated on STN: 12 Aug 1998

L7 ANSWER 41 OF 46 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1998:595067 SCISEARCH
THE GENUINE ARTICLE: 104UY
TITLE: Role for Bcl-x(L) in delayed eosinophil apoptosis mediated by granulocyte-macrophage colony-stimulating factor and **interleukin-5**
AUTHOR: Dibbert B; Daigle I; Braun D; Schranz C; Weber M; Blaser K; ZangemeisterWittke U; Akbar A N; Simon H U (Reprint)
CORPORATE SOURCE: UNIV ZURICH, SWISS INST ALLERGY & ASTHMA RES, SIAF, OBERE STR 22, CH-7270 DAVOS, SWITZERLAND (Reprint); UNIV ZURICH, SWISS INST ALLERGY & ASTHMA RES, SIAF, CH-7270 DAVOS, SWITZERLAND; CLIN DERMATOL & ALLERGY, DAVOS, SWITZERLAND; UNIV ZURICH HOSP, DEPT INTERNAL MED, DIV ONCOL, ZURICH, SWITZERLAND; ROYAL FREE HOSP, SCH MED, DEPT CLIN IMMUNOL, LONDON, ENGLAND
COUNTRY OF AUTHOR: SWITZERLAND; ENGLAND
SOURCE: BLOOD, (1 AUG 1998) Vol. 92, No. 3, pp. 778-783.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399.
ISSN: 0006-4971.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 18
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Eosinophils are potent inflammatory cells involved in allergic reactions. inhibition of apoptosis of purified eosinophils by certain cytokines has been previously shown to be an important mechanism causing tissue eosinophilia. To elucidate the role of Bcl-2 family members in the inhibition of eosinophil apoptosis, we examined the expression of the known anti-apoptotic genes Bcl-2, Bcl-x(L), and Al, as well as Bar and Bcl-x(s), which promote apoptosis in other systems. We show herein that freshly isolated human eosinophils express significant amounts of Bcl-x(L) and Bar, but only little or no Bcl-2, Bcl-x(s), Or Al AS assessed by reverse transcription-polymerase chain reaction, immunoblotting, flow cytometry, and immunocytochemistry, we show that spontaneous eosinophil apoptosis is associated with a decrease in Bcl-x(L) mRNA and protein levels. In contrast, stimulation of the cells with granulocyte-macrophage colony-stimulating factor (GM-CSF) or **interleukin-5** (**IL-5**) results in maintenance or upregulation of Bcl-x(L) mRNA and protein levels. Moreover, Bcl-2 protein is not induced by GM-CSF or **IL-5** in purified eosinophils. Bcl-2 protein is also not expressed in tissue eosinophils as assessed by immunohistochemistry using two different eosinophilic tissue models. Furthermore, Bcl-x(L) **antisense** but not scrambled phosphorothioate oligodeoxynucleotides can partially block the cytokine-mediated rescue of apoptotic death in these cells. These data suggest that Bcl-x(L) acts as an anti-apoptotic molecule in eosinophils. (C) 1998 by The American Society of Hematology.

L7 ANSWER 42 OF 46 MEDLINE on STN DUPLICATE 15
ACCESSION NUMBER: 1999018546 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9801738
TITLE: **Interleukin-5**: a proeosinophil cytokine mediator of inflammation in **asthma** and a target for **antisense** therapy.
AUTHOR: Weltman J K; Karim A S

CORPORATE SOURCE: Department of Medicine, Brown University School of Medicine, Providence, Rhode Island, USA.
SOURCE: Allergy and asthma proceedings : official journal of regional and state allergy societies, (1998 Sep-Oct) 19 (5) 257-61. Ref: 42
Journal code: 9603640. ISSN: 1088-5412.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990202
Last Updated on STN: 19990202
Entered Medline: 19990120

AB **Interleukin-5** (**IL-5**) is the predominant cytokine associated with antigen-induced eosinophilic inflammation in the lung. The activation of TH2 cells leads to the production of **IL-5**. The proeosinophilic effects of **IL-5** include 1) enhanced replication and differentiation of eosinophilic myelocytes; 2) enhanced degranulation of eosinophils; 3) prolonged survival time of eosinophils; and 4) enhanced adhesion of eosinophils. The effects of **IL-5** are mediated via the interaction of **IL-5** with receptors (Il-5R) expressed on the eosinophil cell membrane. Intracellular signaling produced by occupation of the IL-5R by **IL-5** occurs via the JAK-STAT system. **IL-5** is a 45kD glycoprotein that consists of two identical polypeptide chains. The 5'-promoter region of the **IL-5** gene contains elements that are down-regulated by glucocorticoids. A 16-mer deoxyoligonucleotide, **antisense** to **IL-5** mRNA and with two phosphorothioate modifications, produced, at 20 micromolar concentration, complete inhibition of **IL-5** secretion by human peripheral blood mononuclear cells. The targeted 16-mer sequence of the **IL-5** mRNA did not display complete homology with any other known human gene sequences. These results suggest that the 16-mer phosphorothioate **antisense IL-5** provides the basis for a non-glucocorticoid, sequence-specific inhibitor of **IL-5**.

L7 ANSWER 43 OF 46 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1998:114633 SCISEARCH
THE GENUINE ARTICLE: YU762
TITLE: **IL-5** and **IL-5** receptor in **asthma**
AUTHOR: Kotsimbos A T C; Hamid Q (Reprint)
CORPORATE SOURCE: MCGILL UNIV, MEAKINS CHRISTIE LABS, DEPT MED, 3626 RUE ST URBAIN, QUEBEC CITY, PQ H2X 2P2, CANADA (Reprint); MCGILL UNIV, MEAKINS CHRISTIE LABS, DEPT MED, QUEBEC CITY, PQ H2X 2P2, CANADA
COUNTRY OF AUTHOR: CANADA
SOURCE: MEMORIAS DO INSTITUTO OSWALDO CRUZ, (30 DEC 1997) Vol. 92, Supp. [S], pp. 75-91.
Publisher: FUNDACO OSWALDO CRUZ, AV BRASIL 4365, 21045-900 RIO DE JANEIRO, RJ, BRAZIL.
ISSN: 0074-0276.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 156

015 Chest Diseases, Thoracic Surgery and Tuberculosis
026 Immunology, Serology and Transplantation
LANGUAGE: English

L7 ANSWER 46 OF 46 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1998:121914 BIOSIS
DOCUMENT NUMBER: PREV199800121914
TITLE: **IL-5** and **IL-5** receptor in **asthma**.
AUTHOR(S): Kotsimbos, A. T. C.; Hamid, Q. [Reprint author]
CORPORATE SOURCE: Dep. Med., Meakins-Christie Lab., McGill Univ., 3626 rue St. Urbain, Montreal, PQ H2X 2P2, Canada
SOURCE: Memorias do Instituto Oswaldo Cruz, (Dec. 30, 1997 (1998)) Vol. 92, No. SUPPL. 2, pp. 75-91. print.
CODEN: MIOCAS. ISSN: 0074-0276.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Mar 1998
Last Updated on STN: 5 Mar 1998

AB Eosinophils, along with mast cells are key cells involved in the innate immune response against parasitic infection whereas the adaptive immune response is largely dependent on lymphocytes. in chronic parasitic disease and in chronic allergic disease, **IL-5** is predominantly a T cell derived cytokine which is particularly important for the terminal differentiation, activation and survival of committed eosinophil precursors. The human **IL-5** gene is located on chromosome 5 in a gene cluster that contains the evolutionary related IL-4 family of cytokine genes. The human **IL-5** receptor complex is a heterodimer consisting of a unique a subunit (predominantly expressed on eosinophils) and a beta subunit which is shared between the receptors for IL-3 and GM-CSF (more widely expressed). The alpha subunit is required for ligand-specific binding whereas association with the beta subunit results in increased binding affinity. The alternative splicing of the alphaIL-5R gene which contains 14 exons can yield several alphaIL-5R isoforms including a membrane-anchored isoform (alphaIL-5Rm) and a soluble isoform (alphaIL-5Rs). Cytokines such as **IL-5** produce specific and non-specific cellular responses through specific cell membrane receptor mediated activation of intracellular signal transduction pathways which, to a large part, regulate gene expression. The major intracellular signal transduction mechanism is activation of non-receptor associated tyrosine kinases including JAK and MAP kinases which can then transduce signals via a novel family of transcriptional factors named signal transducers and activators of transcription (STATS). JAK2, STAT1 and STAT5 appear to be particularly important in **IL-5** mediated eosinophil responses.
Asthma is characterized by episodic airways obstruction, increased bronchial responsiveness, and airway inflammation. Several studies have shown an association between the number of activated T cells and eosinophils in the airways and abnormalities in FEV1, airway reactivity and clinical severity in **asthma**. It has now been well documented that **IL-5** is highly expressed in the bronchial mucosa of atopic and intrinsic asthmatics and that the increased **IL-5** mPNA present in airway tissues is predominantly T cell derived. Immunocytochemical staining of bronchial biopsy sections has confirmed that **IL5** mRNA transcripts are translated into protein in asthmatic subjects. Furthermore, the number of activated CD4+ T cells and **IL-5** mRNA positive cells are increased in asthmatic airways following antigen challenge and studies that have examined **IL-5** expression in asthmatic subjects before and after steroids have shown significantly decreased expression following

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Eosinophils, along with mast cells are key cells involved in the innate immune response against parasitic infection whereas the adaptive immune response is largely dependent on lymphocytes. in chronic parasitic disease and in chronic allergic disease, **IL-5** is predominantly a T cell derived cytokine which is particularly important for the terminal differentiation, activation and survival of committed eosinophil precursors. The human **IL-5** gene is located on chromosome 5 in a gene cluster that contains the evolutionary related IL-4 family of cytokine genes. The human **IL-5** receptor complex is a heterodimer consisting of a unique a subunit (predominantly expressed on eosinophils) and a beta subunit which is shared between the receptors for IL-3 & GM-CSF(more widely expressed). The a subunit is required for ligand-specific binding whereas association with the beta subunit results in increased binding affinity. The alternative splicing of the alpha IL-5R gene which contains 14 exons can yield several alpha IL-5R isoforms including a membrane-anchored isoform (alpha IL-5Rm) and a soluble isoform (alpha IL-5Rs). Cytokines such as **IL-5** produce specific and non-specific cellular responses through specific cell membrane receptor mediated activation of intracellular signal transduction pathways which, to a large part, regulate gene expression. The major intracellular signal transduction mechanism is activation of non-receptor associated tyrosine kinases including JAK and MAP kinases which can then transduce signals via a novel family of transcriptional factors named signal transducers and activators of transcription (STATS). JAK2, STAT1 and STAT 5 appear to be particularly important in IL-S mediated eosinophil responses.

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transferred by CD4+ but not CD8+ T cells in putts. The importance of **IL-5** in animal models of allergen induced bronchial hyperresponsiveness has been further demonstrated by a number of studies which have indicated that **IL-5** administration is able to induce late phase responses and BHR and that anti-**IL-5** antibody can block allergen induced late phase responses and BHR.

In summary, activated T lymphocytes, **IL5** production and eosinophil activation air particularly important it the asthmatic response. Human studies in **asthma** and studies in allergic animal models have clear Ey emphasised the unique role of 1L-5 in linking T lymphocytes and adaptive immunity the eosinophil effector-cell, and the **asthma** phenotype. The central role of activated lymphocytes and eosinophils in **asthma** would argue for the likely therapeutic success of strategies to block T cell and eosinophil activation (eg steroids), Importantly more targeted therapies may avoid the complications associated with steroids. Such therapies could target key T cell activation proteins and cytokines by various means including blocking antibodies (eg anti-CD4, anti-CD40, anti-**IL-5** etc), **antisense** oligonucleotides to their specific mRNAs, and/or selective inhibition of the promoter sites for these genes. Another option would be to target key eosinophil activation mechanisms including the alpha IL5r. As always, the risk to benefit ratio of such strategies await the results of,cell conducted clinical trials.

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ACCESSION NUMBER: 95174281 EMBASE
DOCUMENT NUMBER: 1995174281
TITLE: Advances in molecular genetics, transgenic models, and gene therapy for the study of pulmonary diseases.
AUTHOR: Mossman B.T.; Mason R.; McDonald J.A.; Gail D.B.
CORPORATE SOURCE: Division of Lung Diseases, Natl. Heart, Lung, and Blood Inst., National Institutes of Health, 6701 Rockledge Drive,Bethesda, MD 20892-7952, United States
SOURCE: American Journal of Respiratory and Critical Care Medicine, (1995) 151/6 (2065-2069).
ISSN: 1073-449X CODEN: AJCMED
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
022 Human Genetics
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English

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ACCESSION NUMBER: 94360116 EMBASE
DOCUMENT NUMBER: 1994360116
TITLE: Cytokines as mediators of chronic **asthma**.
AUTHOR: Barnes P.J.
CORPORATE SOURCE: Department of Thoracic Medicine, National Heart and Lung Institute, Dovehouse Street,London SW3 6LY, United Kingdom
SOURCE: American Journal of Respiratory and Critical Care Medicine, (1994) 150/5 II (S42-S49).
ISSN: 1073-449X CODEN: AJCMED
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
006 Internal Medicine

STIC

oral corticosteroid treatment in steroid-sensitive **asthma** but not in steroid resistant and chronic severe steroid dependent **asthma**. The link between T cell derived **IL-5** and eosinophil activation in asthmatic airways is further strengthened by the demonstration that there is an increased number of alphaIL-5R mRNA positive cells in the bronchial biopsies of atopic and non-atopic asthmatic subjects and that the eosinophil is the predominant site of this increased alphaIL-5R mRNA expression. We have also shown that the subset of activated eosinophils that expressed mRNA for membrane bound alphaIL5r inversely correlated with FEV1, whereas the subset of activated eosinophils that expressed mRNA for soluble alphaIL5r directly correlated with FEV1. Hence, not only does this data suggest that the presence of eosinophils expressing alphaIL-5R mRNA contribute towards the pathogenesis of bronchial **asthma**, but also that the eosinophil phenotype with respect to alpha IL5R isoform expression is of central importance. Finally, there are several animal, and more recently in vitro lung explant, models of allergen induced eosinophilia, late airway responses (LARS), and bronchial hyperresponsiveness (BHR) - all of which support a link between **IL-5** and airway eosinophila and bronchial hyperresponsiveness. The most direct demonstration of T cell involvement in LARS is the finding that these physiological responses can be transferred by CD4+ but not CD8+ T cells in rats. The importance of **IL-5** in animal models of allergen induced bronchial hyperresponsiveness has been further demonstrated by a number of studies which have indicated that **IL-5** administration is able to induce late phase responses and BHR and that anti-**IL-5** antibody can block allergen induced late phase responses and BHR. In summary, activated T lymphocytes, **IL5** production and eosinophil activation are particularly important in the asthmatic response. Human studies in **asthma** and studies in allergic animal models have clearly emphasized the unique role of **IL-5** in linking T lymphocytes and adaptive immunity, the eosinophil effector cell, and the **asthma** phenotype. The central role of activated lymphocytes and eosinophils in **asthma** would argue for the likely therapeutic success of strategies to block T cell and eosinophil activation (e.g. steroids). Importantly, more targeted therapies may avoid the complications associated with steroids. Such therapies could target key T cell activation proteins and cytokines by various means including blocking antibodies (e.g. anti-CD4, anti-CD40, anti-**IL-5** etc), **antisense** oligonucleotides to their specific mRNAs, and/or selective inhibition of the promoter sites.for these genes. Another option would be to target key eosinophil activation mechanisms including the alphaIL5r. As always, the risk to benefit ratio of such strategies await the results of well conducted clinical trials.

=> D L6 IBIB ABS 1-3

L6 ANSWER 1 OF 3 MEDLINE on STN
ACCESSION NUMBER: 2004053777 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14754517
TITLE: New **asthma** drugs acting on gene expression.
AUTHOR: Popescu F-D
CORPORATE SOURCE: Department of Allergology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania.. florindanpopescu@hotmail.com
SOURCE: Journal of cellular and molecular medicine, (2003 Oct-Dec) 7 (4) 475-86. Ref: 31
Journal code: 101083777. ISSN: 1582-1838.
PUB. COUNTRY: Romania
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200404
ENTRY DATE: Entered STN: 20040203
Last Updated on STN: 20040416
Entered Medline: 20040415

AB New **asthma** drugs acting on transcription are transcription factor agonists (dissociated steroids, peroxisome proliferator-activated receptor gamma agonists), transcription factor inhibitors (NF-kappaB / AP-1 inhibitors, STAT6 inhibitors), inhibitors of protein kinases acting on transcription factors (p38 MAP kinase inhibitors), and chromatin modifying agents. Pharmacological approach of translation in **asthma** includes therapeutic **ribozymes** and **antisense** oligonucleotides targeting receptors (adenosine A1 receptor, alpha chain of **IL-5** receptor, common beta chain of IL-3/**IL-5**/GM-CSF receptor), cytokines (IL-4, **IL-5**, SCF), signal transduction molecules (Syk, Lyn), transcription factors (STAT-6, GATA-3). Some of these drugs acting on gene expression have the potential to improve therapeutic benefits compared with traditional drugs.

L6 ANSWER 2 OF 3 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 95174281 EMBASE
DOCUMENT NUMBER: 1995174281
TITLE: Advances in molecular genetics, transgenic models, and gene therapy for the study of pulmonary diseases.
AUTHOR: Mossman B.T.; Mason R.; McDonald J.A.; Gail D.B.
CORPORATE SOURCE: Division of Lung Diseases, Natl. Heart, Lung, and Blood Inst., National Institutes of Health, 6701 Rockledge Drive,Bethesda, MD 20892-7952, United States
SOURCE: American Journal of Respiratory and Critical Care Medicine, (1995) 151/6 (2065-2069).
ISSN: 1073-449X CODEN: AJCMED
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FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
022 Human Genetics
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English

L6 ANSWER 3 OF 3 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2004:942761 SCISEARCH
THE GENUINE ARTICLE: 863CO
TITLE: New **asthma** drugs acting on gene expression
AUTHOR: Popescu F D (Reprint)
CORPORATE SOURCE: Nicolac Malaxa Hosp, Dept Allergol, 12 Sos Verguhui, Bucharest, Romania (Reprint); Carol Davila Univ Med & Pharm, Dept Allergol, Bucharest, Romania
COUNTRY OF AUTHOR: Romania
SOURCE: JOURNAL OF CELLULAR AND MOLECULAR MEDICINE, (OCT-DEC 2003) Vol. 7, No. 4, pp. 475-486.
Publisher: CAROL DAVILA UNIV PRESS, 8 EROILOR SANITARI BLVD, BUCHARESST 76241, ROMANIA.
ISSN: 1582-1838.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English

REFERENCE COUNT: 31

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB New **asthma** drugs acting on transcription are transcription factor agonists (dissociated steroids, peroxisome proliferator-activated receptor gamma agonists), transcription factor inhibitors (NF-kappaB / AP-1 inhibitors, STAT6 inhibitors), inhibitors of protein kinases acting on transcription factors (p38 MAP kinase inhibitors), and chromatin modifying agents. Pharmacological approach of translation in **asthma** includes therapeutic **ribozymes** and **antisense** oligonucleotides targeting receptors (adenosine A1 receptor, alpha chain of **IL-5** receptor, common beta chain of IL-3/**IL-5**/GM-CSF receptor), cytokines (IL-4, **IL-5**, SCF), signal transduction molecules (Syk, Lyn), transcription factors (STAT-6, GATA-3). Some of these drugs acting on gene expression have the potential to improve therapeutic benefits compared with traditional drugs.